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Trastuzumab Biosimilars: Evaluating their Potential for Fda Interchangeability

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ABSTRACT: Herceptin (trastuzumab) has been the backbone of HER2-positive breast and gastric cancer treatment since 1998. Several biosimilar versions now have regular FDA approval. But none are designated "interchangeable" by the Food and Drug Administration, a classification that allows a pharmacist to substitute a biosimilar without consulting the prescriber first. This review fills this gap: does the evidence already collected on trastuzumab biosimilars meet the interchangeability bar set by the 2009 Biologics Price Competition and Innovation Act? The scope is intentionally limited. Rather than re-litigating the clinical outcomes in detail, the paper reviews existing analytical, pharmacokinetic, clinical and post-marketing data against each of the regulatory requirements in turn, relying on FDA guidance, statutory language, agency records and literature published through March 2026. But one development changes the calculus significantly: The FDA draft guidance in June 2024 abandoned the long-standing expectation of a dedicated switching study. Two approvals since then are a reflection of what that shift looks like in practice. Four biosimilar denosumab products received approval as interchangeable in October 2025. Then, in November 2025, Poherdy (pertuzumab-dpzb), an antibody usually given with trastuzumab itself, was approved as the first interchangeable biosimilar in oncology. So where does this leave trastuzumab? The technical requirements case looks strong: analytical similarity, pharmacokinetic comparability and matched clinical efficacy and safety have all been demonstrated for approved products. Data switching is not necessary but its safety is supported by real-world cohorts from Sweden, Brazil and China. The unsettled is narrower: can a sponsor lean on data already sitting in an existing biologics license application, will oncology be judged by the same yardstick as the non-oncology cases so far, and how much will state-by-state differences in pharmacy substitution law blunt the real-world effect once a designation does land. The bottom line: the approval of pertuzumab brings the runway for trastuzumab interchangeability much closer than it looked even a year ago — although nothing is settled until a sponsor actually files and the FDA rules.

1. INTRODUCTION

1.1 What Are Biosimilars and Why Do They Matter? Biologics serve as huge, complicated chemicals that are the foundation of many current treatments across multiple therapeutic areas. They are made from living cells, not by chemical synthesis. This manufacturing complexity has a real cost: high development costs and high final prices for patients make them unaffordable for a large percentage of those who would benefit.[1],[2]

The initial step in defining a biosimilar is to point out that it is not an exact copy. This biotherapeutic is a biosimilar with an already approved innovator product. This is a major difference, as unlike a small-molecule generic, a biosimilar can not be easily made to match; living systems can not reproduce with the same precision as a chemical reaction. A developer must

instead show through analytical, non-clinical and clinical testing that the product is within a reasonable margin of the reference product on all relevant metrics.[3][4][5][6]

Biosimilars gain traction in health care policy via competition. When a patent on a reference product expires, the launch of a biosimilar reduces prices and improves access. This is not just theory; two biosimilar monoclonal antibodies, rituximab and trastuzumab, have already delivered real savings in several health systems.[7][8][9][10]

But none of this means the transition from originator to biosimilar is automatic. But there are still concerns about immunogenicity, doctors and patients don't always embrace the concept at the same rate, and interchangeability guidelines aren't consistent enough to resolve the issue completely.[11]

1.2 Trastuzumab: Background and Clinical Role

Trastuzumab (Herceptin®) was designed to target HER2, a protein that is overexpressed in approximately one in five to one in four cases of breast cancer and is strongly correlated with the tumors' rate of growth. Since being on sale in 1998, the medication has significantly improved survival rates for HER2-positive breast cancer, both in the early stages of the disease and after it has progressed.[7] [12][13]

The other main indicator is gastric cancer. There, as in breast cancer, trastuzumab is usually used in conjunction with chemotherapy and frequently with pertuzumab, another HER2-targeted antibody. The pattern is pretty consistent throughout stages: trastuzumab plus a taxane is the recommended first-line treatment in the metastatic context, whereas a year of adjuvant trastuzumab reduces the risk of recurrence and death in early illness.[7][14]

In actuality, all of this is constrained by cost. Many healthcare systems are unable to afford trastuzumab due to its high cost, which is precisely the reason biosimilar versions were created in the first place.[15],[16]

1.3 The Interchangeability Designation: An Overview

Interchangeability is a regulatory term imported by the BPCIA in 2009 that has remained uniquely American ever since. The bar is even higher than for regular biosimilarity: A product must not only meet all the standard biosimilar requirements, but also be expected to produce the same clinical outcome as the reference product, regardless of which patient receives it. There cannot be more risk switching between the two than continued use of the reference product for everything dosed more than once.[17] [18] [19] If you can get past that hurdle, the real upside is that where state law allows, the pharmacist can dispense the biosimilar instead of the reference medicine without first consulting the prescriber. This is almost exactly how generic substitution works today.[20] It is worth mentioning that no other place works this way. In 2022, the European Medicines Agency (EMA) and European national authorities have said that biosimilars approved in the EU could in many cases be considered interchangeable on scientific grounds. But unlike the United States, the EU never created a formal legal category for it, leaving pharmacy-level substitution decisions to each member state.[21]

Until recently the entire field of oncology was outside this category. In November 2025, the FDA approved Poherdy (pertuzumab-dpzb), a replacement for Perjeta (pertuzumab), an antibody targeting HER2 that is used in combination with trastuzumab in standard dual-blockade regimens for HER2-positive breast cancer.[22]

Some trastuzumab biosimilars are approved as standard, but not here yet. The present paper aims at addressing this gap by reviewing the available clinical, regulatory and analytical evidence on the future of trastuzumab in contrast with recent precedents, denosumab and, more especially, pertuzumab.[3] [23] [22]

2. MATERIALS AND METHODS

2.1 Search Strategy and Sources

This review used a regulatory-focused narrative review approach rather than a systematic clinical review, given that the central research question concerns regulatory pathway requirements rather than treatment efficacy in isolation. Two categories of sources were consulted.

Primary regulatory documents: FDA draft and final guidance documents on biosimilar interchangeability, the relevant statutory provisions of the BPCIA, and FDA approval records and press releases announcing interchangeable biosimilar designations, including those for denosumab and pertuzumab biosimilars.[17][18][19][24][3][22]

Peer-reviewed and trade literature: PubMed, Scopus, and the Cochrane Library were searched using terms including "trastuzumab biosimilar," "interchangeability," "FDA guidance," "denosumab interchangeable," "pertuzumab interchangeable," and "biosimilar substitution law." Trade and regulatory news sources (e.g., GaBI Online, Clinical Trials Arena, the Center for Biosimilars, AJMC) were additionally consulted to capture regulatory developments from 2024–2026 not yet reflected in peer-reviewed literature.

A small number of supplementary sources were consulted to confirm a single comparative point regarding the absence of an equivalent interchangeability category outside the United States; this point is used only as brief contextual background in Section 1.3 and is not developed into a comparative analysis.

2.2 Search Period

The searches were performed from January 2015, the date of the first biosimilar approval by the FDA, to March 2026, focusing on regulatory decisions after the FDA's draft guidance on interchangeability (June 2024), and subsequent interchangeability approvals through late 2025.

2.3 Selection Criteria

Sources were included if they addressed one or more of the following: (1) FDA requirements for biosimilar or interchangeable biosimilar designation; (2) the BPCIA interchangeability standard; (3) the regulatory status of trastuzumab biosimilars; (4) precedent-setting interchangeability decisions for other biologics, especially monoclonal antibodies; or (5) U.S. state-level pharmacy substitution statutes. Picking through the clinical trial data just enough to see if the current evidence meets a specific regulatory need, rather than doing a full clinical evaluation.

2.4 Analytical Framework

The available evidence for trastuzumab biosimilars was mapped to each of the requirements under the BPCIA interchangeability standard to determine whether the requirement is met, or no longer required, or remains an open gap. The cornerstone analytical approach of this review is the requirement-by-requirement comparison summarized in Table 3.

2.5 Limitations of the Approach

This narrative regulatory review was not a systematic review and was not conducted under PRISMA protocol, including independent dual-reviewer screening, and may not reflect unpublished agency communications, internal FDA deliberations, or pending applications not yet part of the public record.

3. REGULATORY FRAMEWORK FOR INTERCHANGEABILITY

3.1 The U.S. Biosimilar Approval Pathway (FDA)

Safety, efficacy, and quality are not assumed once a biosimilar is introduced into clinical practice in the US. This is exactly what the regulatory framework, which is based on the BPCIA of 2009 (and has been in effect through FDA guidance since approximately 2015) is meant to do: determine these factors before a product reaches patients. In practice it is a robust comparison to the reference biologic that includes clinical efficacy testing, pharmacokinetic and pharmacodynamic matching, analytical characterisation and an immunogenicity check.[3][5][6][7]

Table 1 lays out what that evidentiary package looks like for standard FDA biosimilar approval

Table 1. FDA Biosimilar Approval Requirements

Evidentiary Component	Requirement
Analytical similarity	Demonstrated highly similar structure and function relative to reference product
Non-clinical/animal data	Toxicity and immunogenicity assessment, as needed
PK/PD studies	Comparable systemic exposure relative to reference product

Immunogenicity assessment	Comparable immune response profile
Comparative clinical efficacy	At least one adequately powered study showing no clinically meaningful differences

3.2 The BPCIA Interchangeability Standard

The interchangeability in the BPCIA hierarchy is above the ordinary biosimilarity with two more requirements. First, the same clinical outcome is expected as the reference product irrespective of the patient receiving the product. Second, for anything given more than once, the switch from the biosimilar to the reference product cannot be more dangerous than continuing on the reference product.[17][18][19]

That matters because once a product meets that standard, a pharmacist can substitute the reference product at the counter without consulting the doctor, but the details still are governed by state law. It is like replacing trade-name drugs with nonproprietary drugs. In addition to the basic biosimilarity requirements, the interchangeability criterion is defined in Table 2.[17][18][19][4]

Table 2. Requirements for Biosimilar vs. Interchangeable Designation

Requirement	**Biosimilar**	**Interchangeable**
Analytical similarity	Required	Required
PK/PD comparability	Required	Required
Comparative clinical efficacy	Required (≥1 study)	Required
Clinical immunogenicity	Required	Required
Same clinical result in any given patient	Not required	Required
Switching-risk evidence	Not required	Previously required via dedicated study; no longer categorical since June 2024
Pharmacy-level substitution	Not permitted	Permitted, subject to state law

3.3 The 2024 Guidance Reform: Eliminating Switching Studies

The FDA's draft guidance in June 2024 upended the interchangeability landscape by stating that it would no longer impose a dedicated switching study as a categorical requirement for interchangeability determinations in general.[4]

The change was motivated by the accumulation of evidence indicating that comparative efficacy and switching studies (often taking 1 to 3 years and costing tens of millions of dollars) are generally less sensitive than modern analytical methods in detecting clinically meaningful differences; that analytical and pharmacokinetic equivalence often provides sufficient assurance to predict clinical behavior; and that real-world evidence across a spectrum of therapeutic areas has independently corroborated the safety of switching.[20][7]

The FDA remains committed to a "totality of the evidence" approach, where the specific evidence needed is determined on a case-by-case basis rather than against a fixed checklist, but the categorical expectation of a dedicated switching study has been removed for many products.[10]

3.4 Supporting Precedents: Denosumab and Pertuzumab Interchangeable Approvals

Since then, two FDA rulings provide direct answers to the question of whether the post-2024 paradigm really holds up for complicated antibodies. Four denosumab biosimilars, including Celltrion's Stoboclo® and Osenvelt®, were granted interchangeable status in October 2025 after gaining approval against Prolia® and Xgeva® due to the strength of available BLA data, analytical similarity, and comparative clinical evidence. No independent switching study was performed.[3]

Here, the case for pertuzumab is more important. Poherdy (pertuzumab-dpzb), a HER2-targeted antibody typically used in combination with trastuzumab and chemotherapy in standard treatment regimens, was the first interchangeable oncology biosimilar approved by the FDA in November 2025. The approval was based on relatively limited evidence that included one study on analytical comparability, one pharmacokinetic study in healthy volunteers, and one clinical study in patients with early-stage neoadjuvant disease. [22] Again, no specific research on switching.

Although they are not distant cousins as both trastuzumab and pertuzumab are HER2 targeted IgG1 monoclonal antibodies, and are commonly used in similar regimens. That's why this precedent is more relevant than the denosumab approvals. And it also challenges a long-held belief that the evidentiary standard for interchangeability would always be higher for cancer biosimilars than for anything else.[22]

3.5 Post-Marketing Surveillance Requirements

Post-marketing pharmacovigilance plays an ongoing role in monitoring biosimilar safety post-approval, regardless of interchangeable status. Long-term safety outcomes, immunogenicity across different populations, cardiac safety (LVEF monitoring), rare adverse events and effectiveness in real-world settings are continued surveillance priorities for trastuzumab biosimilars.[1],[6],[7],[25]

Pharmacovigilance plans are a standing condition of approval for the FDA, and real-world data could be a supplement to, but not a substitute for, the formal interchangeability evidence package.[1] [19]

4. GAP ANALYSIS: TRASTUZUMAB BIOSIMILARS AGAINST THE INTERCHANGEABILITY CHECKLIST

4.1 Requirements Already Satisfied

It appears that part of the interchangeability checklist has already been ticked off. Ogivri, Herzuma, Ontruzant, Trazimera, Kanjinti — every trastuzumab biosimilar on the market today had to demonstrate analytical similarity to get their initial biosimilar approval. PK/PD match for each was seen in phase 1 studies with phase 3 trials such as SB3, CTP6, MYL1401O, HLX02 and BP02 confirming with comparable response rates, progression free survival and overall survival against reference trastuzumab. [7] [8] [11]

Immunogenicity was also checked in those trials and in the years of follow-up since, and came back comparable. All of this is already in the biologics license application for every product, no redoing needed.[1][6][7]

4.2 Requirements No Longer Required Following the 2024 Reform

The dedicated switching study has long been the single most significant practical barrier to interchangeability; but as of the FDA's June 2024 rule, it is no longer required as a categorical necessity. [7]

The same conclusion is supported by real world switching data from Sweden, Brazil, and China. It is not from a formal switching trial, but the FDA has demonstrated a willingness to consider support for real-world evidence under a totality-of-the-evidence approach.[25][11]

4.3 Remaining Uncertainties and Open Questions

But none of this leads to a firm conclusion; there are still a few real questions left and this study treats them as such, rather than assuming trastuzumab will be successful.

One is if a sponsor can ask for interchangeability for a trastuzumab biosimilar that has already been approved via BLA without producing new clinical or analytical data. Yes, as seen with the denosumab and pertuzumab examples, but no actual challenge

has been filed by any of the trastuzumab sponsors and the FDA considers each application on its own merits under the totality-of-the-evidence approach.[3] [22]

Secondly, while the approval of pertuzumab raises questions about the long held view that oncology necessarily demands a higher standard of proof, it does not eliminate additional scrutiny. The dual role of the combination of pertuzumab doesn't quite answer the question of whether a drug with only a curative intent would be treated similarly by the FDA and a curative or survival intent indication has more consequences if efficacy quietly wanes after a switch. Open question, not closed question.[22]

third: To the best of the authors' knowledge, none of the sponsors of trastuzumab biosimilars have publicly announced that they are submitting an application for interchangeability. The existence of a regulatory pathway, in theory, does not tell us if anyone is taking it or not.

Four: The FDA decision aside, uptake could vary greatly from state to state because of the broad differences in state pharmacy substitution laws (see Section 6.3). A successful FDA designation does not guarantee a consistent real-world impact. [11][19]



Figure 1. Status of each interchangeability requirement for trastuzumab biosimilars, based on the gap analysis in Sections 4.1–4.3

4.4 Summary Table

Table 3. Trastuzumab Biosimilar Interchangeability Requirements — Current Status and Gaps

Requirement	Current Status	Gap Assessment
Analytical similarity	Established for all approved biosimilars	No gap
PK/PD comparability	Demonstrated in phase 1 trials	No gap
Clinical efficacy equivalence	Confirmed in phase 3 trials	No gap
Clinical immunogenicity	Comparable profiles demonstrated	No gap
Switching-risk evidence	Not formally required since June 2024; real-world data available (Sweden, Brazil, China)	Supportive evidence exists; no dedicated study conducted or required
Use of existing BLA data without new submissions	Plausible based on denosumab/pertuzumab precedent	Untested for trastuzumab specifically

Oncology-specific regulatory scrutiny	Pertuzumab precedent suggests parity with non-oncology approvals	Not yet confirmed for a curative/adjuvant-intent oncology indication
Sponsor application	None publicly announced	Open; no filing identified
State-level substitution implementation	Highly variable by state	Independent of FDA designation; affects real-world impact only

5. SUPPORTING EVIDENCE

5.1 Clinical Evidence Summary

And when you combine phase 3 trials, years of follow-up, meta-analyses, and real-world cohorts, the bottom line is the same: the trastuzumab biosimilars are clinically equivalent to the reference trastuzumab. In a Cochrane analysis of 55 studies and more than 22,000 patients, there was no discernible difference between the biosimilar and originator in progression-free and overall survival in significant adverse event.[2]

The results of each trial are consistent. SB3, CTP6, MYL1401O, HLX02 and BP02 all demonstrated similar efficacy and a stable and controllable safety profile including immunogenicity. This was also extended to HER2-positive gastric cancer by the CTP6 KSCC TROX study.[7][14]

The clinical evidence base meets the clinical part of the interchangeability requirement as described in Section 4.1. The contribution of this review is the regulatory gap analysis, not a rehash of the clinical literature, and as such it is not purposefully walked through trial by trial.

5.2 Economic Impact Summary

One of the big reasons this matters is money. Modeling of the budget impact across the EU5 estimates that the adoption of IV biosimilars could result in savings of between €19 million and €172 million over a five-year time horizon. Trastuzumab biosimilars may cost 20-40% less than the original product.[13],[2]

And scale that up, and the numbers become startling. In a simulation of the Medicare population in 2025, full conversion to a trastuzumab biosimilar could save >$1000 per patient per month, enough to treat >28,000 additional patients with early-stage breast cancer annually without increasing the budget.[13]

There is also reason to believe that an interchangeable designation would accelerate this. In other instances, interchangeable status has significantly sped up biosimilar uptake (see Section 6.3). So if trastuzumab biosimilars were to achieve that status, the anticipated savings would likely be realized more rapidly than through standard biosimilar approval alone.[19]

6. CHALLENGES AND BARRIERS

6.1 Physician-Related Barriers

In many practice settings, physician familiarity and confidence in the originator product continues to impede trastuzumab biosimilar adoption. Real-world and trial evidence has been reassuring, but surveys of oncologists have highlighted remaining concerns about switching. Any regulatory designation remains an important complement to targeted education for health care professionals.[2]

6.2 Patient-Related Barriers

Patients are more engaged in treatment decisions and patient perceptions of biosimilars can affect adherence and outcomes. The terminology is unfamiliar, requiring clear, accessible patient education materials to build confidence in biosimilar and interchangeable products.[2]

6.3 Variability in State-Level Substitution Laws

That is a state matter, not an FDA interchangability classification . What happens at the pharmacy counter? The authority to substitute is governed by state pharmacy laws, not federal law, and each of the 50 states, Washington D.C. and Puerto Rico have written their own version of this law. They don't quite agree with each other.[19]

In four states – Alabama, Indiana, South Carolina, Washington and Puerto Rico – the prescriber must still approve any substitution before it happens. In six states and Washington, D.C., it is only allowed when the patient does not pay any extra money. No prescriber check-in needed in the remaining roughly 40 states where pharmacists can substitute automatically.[2] Notification rules create another inconsistency with different deadlines and recordkeeping requirements. In some states the pharmacist must inform the physician; in others the patient must be informed. At least twelve states explicitly require patient notification.

This is reflected in actual prescribing trends, not just differences in paperwork. A 2025 cohort study of the interchangeable insulin biosimilar (insulin glargine-yfgn) found that soon after the interchangeable medication was introduced, there was a difference in adoption of nearly seven percentage points between patients in loosely governed states and in more stringent states.[26] Assuming the same for trastuzumab, even if an FDA designation is approved, the adoption would probably follow the same pattern of state by state. This is a different implementation-level question than the regulatory pathway discussed in Section [4] .

6.4 Cost-Related Barriers

The cost of anticancer monoclonal antibodies remains high relative to the budgets of many health systems. This is a challenge for public and private payers, even as biosimilars are reducing list prices by an estimated 20–40%. Persistent barriers are payer formulary design, rebate structures that favour the originator products, and pharmacy benefit manager incentives not always aligned with biosimilar uptake regardless of an interchangeability designation.[2][16]

7. FUTURE PERSPECTIVES

7.1 Regulatory and Policy Reforms

The FDA's June 2024 guidance reform, along with the October 2025 denosumab and November 2025 pertuzumab interchangeability approvals, indicates a long-term move to a more streamlined interchangeability pathway for complex biologics, including monoclonal antibodies.[5],[3],[22]

Additional clarification from the FDA, specifically regarding the use of existing BLA data without additional submissions, would be a significant step in reducing the remaining uncertainty for sponsors contemplating an interchangeability application for trastuzumab biosimilars.

7.2 Expanding Biosimilar Applications

If a trastuzumab biosimilar were granted interchangeable status, it would set a second more closely analogous oncology precedent with pertuzumab, and would likely speed up interchangeability applications for other cancer monoclonal antibodies, including rituximab and bevacizumab biosimilars.[20],[9]

7.3 Implications for Other Oncology Monoclonal Antibodies

Notably, the pertuzumab precedent indicates that the historical assumption of a categorically higher evidentiary bar for oncology biosimilars may not hold under the post-2024 framework. Further surveillance of sponsor activity and additional oncology interchangeability filings will be necessary to determine whether this precedent extends beyond HER2-targeted antibodies given as part of combination regimens.[22]

8. LIMITATIONS OF THIS REVIEW

Some limitations of this review are: First, because this is a narrative review rather than a systematic review, source selection involved some investigator judgment and did not use a formal PRISMA style protocol. A structured systematic review with dual independent screening may identify additional relevant sources.

Second, the regulatory environment discussed here is evolving quickly: this review captures the state of FDA guidance and precedent as of March 2026, and later guidance, approvals, or sponsor filings could materially alter the gap analysis provided in Section 4.

Thirdly, the primary real world switching data used (the Swedish cohort) used a relatively small sample of 48 patients and broader, larger scale switching data specific to trastuzumab would increase confidence in the conclusions of this review.[7]

Fourth, this review concentrated solely on the U.S. regulatory pathway; while this scope was a deliberate choice given the U.S.-specific nature of the interchangeability designation, it means that the review does not assess parallel developments in other jurisdictions in any depth.

Finally, the conclusions of this review are, by necessity, forward-looking in that no biosimilar sponsor of trastuzumab has yet applied for interchangeability and should be viewed as an assessment of regulatory readiness rather than a prediction of approval timing or outcome.

9. CONCLUSION

This evaluation was motivated by a specific question: might trastuzumab biosimilars pass the FDA's interchangeability standard, and if not, what's really lacking? Not so much in terms of technology. Analytical similarity, pharmacokinetic comparability, matched efficacy and safety, and comparable immunogenicity are all already documented in the approved biosimilar submissions.

In June 2024, the one requirement that used to halt this discussion a dedicated switching study was eliminated.[5]Without conducting a formal trial, real-world cohorts from Sweden, Brazil, and China have partially filled that gap.

Two things that are important here came after that shift in direction. Denosumab biosimilars achieved interchangeable status in October 2025, proving the effectiveness of the new framework for complicated monoclonal antibodies in general.[3]In November of that year, pertuzumab (Poherdy), when used in conjunction with trastuzumab in identical regimens, became the first interchangeable oncology biosimilar.[22] Compared to when this review started, that is a far closer precedent.

What is actually left open, then? Not science. "It's a question of whether a sponsor actually files and how the FDA applies its own "totality of the evidence" standard to a medication used in adjuvant and curative settings, where a mistake matters more." Although there is still some uncertainty, it is not as great as it appeared prior to pertuzumab's approval.

The cost and access benefits that have already preceded the regular use of biosimilars would probably accelerate if they were labeled as interchangeable. However, whether that actually occurs depends on how permissive or restrictive each state's substitution statute is, which is described in Section 6.3.

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REFERENCE

[1] Bloomfield D, D'Andrea E, Nagar S, Kesselheim A. Characteristics of Clinical Trials Evaluating Biosimilars in the Treatment of Cancer. JAMA Oncol 2022;8:537. https://doi.org/10.1001/jamaoncol.2021.7230.
[2] Luo X, Du X, Li Z, Liu J, Lv X, Li H, et al. Clinical Benefit, Price, and Uptake for Cancer Biosimilars vs Reference Drugs in China. JAMA Netw Open 2023;6:e2337348. https://doi.org/10.1001/jamanetworkopen.2023.37348.

[3] Yang J, Yu S, Yang Z, Yan Y, Chen Y, Zeng H, et al. Efficacy and Safety of Anti-cancer Biosimilars Compared to Reference Biologics in Oncology: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. BioDrugs 2019;33:357–71. https://doi.org/10.1007/s40259-019-00358-1.
[4] Jacobs I, Ewesuedo R, Lula S, Zacharchuk C. Biosimilars for the Treatment of Cancer: A Systematic Review of Published Evidence. BioDrugs 2017;31:1–36. https://doi.org/10.1007/s40259-016-0207-0.
[5] Díaz LP, Millán S, Chaban N, Campo A del, Spitzer E. Current State and Comparison of the Clinical Development of Bevacizumab, Rituximab and Trastuzumab Biosimilars. Future Oncology 2021;17:2529–44. https://doi.org/10.2217/fon-2020-0923.
[6] Audran R, Chtioui H, Thierry AC, Mayor CE, Vallotton L, Dao K, et al. Immunomodulation profile of the biosimilar trastuzumab MYL-1401O in a bioequivalence phase I study. Sci Rep 2024;14:12872. https://doi.org/10.1038/s41598-024-61265-2.
[7] Triantafyllidi E, Triantafillidis JK. Systematic Review on the Use of Biosimilars of Trastuzumab in HER2+ Breast Cancer. Biomedicines 2022;10:2045. https://doi.org/10.3390/biomedicines10082045.
[8] Barbier L, Declerck P, Simoens S, Neven P, Vulto AG, Huys I. The arrival of biosimilar monoclonal antibodies in oncology: clinical studies for trastuzumab biosimilars. Br J Cancer 2019;121:199–210. https://doi.org/10.1038/s41416-019-0480-z.
[9] Wyrwicz L, Rodríguez Sánchez CA, Sánchez-Rovira P, Lewis S, Sandschafer D, San T. Real-world clinical scenarios during introduction of trastuzumab biosimilar for HER2-positive breast cancer in the European Union. Future Oncology 2024;20:821–32. https://doi.org/10.2217/fon-2023-0421.
[10] Brown JR, Cymbalista F, Sharman J, Jacobs I, Nava-Parada P, Mato A. The Role of Rituximab in Chronic Lymphocytic Leukemia Treatment and the Potential Utility of Biosimilars. Oncologist 2018;23:288–96. https://doi.org/10.1634/theoncologist.2017-0150.
[11] Song NK, Musa H, Soriano M, Hibbs DE, Ramzan I, Ong JA. Safety of Rituximab biosimilar (Riximyo®) following a single switch from the reference product in patients with Non-Hodgkin's lymphoma: a retrospective study. Ann Hematol 2024;103:4607–12. https://doi.org/10.1007/s00277-024-05981-9.
[12] Nearchou A, Valachis A, Upveja KH. Abstract P5-07-21: Real-World Safety and Effectiveness of Switching among Biosimilars in HER2-Positive Breast Cancer. Clinical Cancer Research 2025;31:P5-07-21-P5-07–21. https://doi.org/10.1158/1557-3265.SABCS24-P5-07-21.
[13] GIULIANI J, BONETTI A. The Economic Impact of Biosimilars in Oncology and Hematology: The Case of Trastuzumab and Rituximab. Anticancer Res 2019;39:3971–3. https://doi.org/10.21873/anticanres.13552.
[14] Yamada T, Nakashima Y, Kashiwada T, Sonoda H, Hattori M, Kawanaka H, et al. A multicenter randomized phase II study of trastuzumab biosimilar (CT-P6) and chemotherapy (SOX or CapeOX) in HER2-positive advanced/recurrent gastric cancer (KSCC: TROX study). Journal of Clinical Oncology 2025;43:4029–4029. https://doi.org/10.1200/JCO.2025.43.16_suppl.4029.
[15] Lammers P, Criscitiello C, Curigliano G, Jacobs I. Barriers to the Use of Trastuzumab for HER2+ Breast Cancer and the Potential Impact of Biosimilars: A Physician Survey in the United States and Emerging Markets. Pharmaceuticals 2014;7:943–53. https://doi.org/10.3390/ph7090943.
[16] Cherny N, Sullivan R, Torode J, Saar M, Eniu A. ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe. Annals of Oncology 2016;27:1423–43. https://doi.org/10.1093/annonc/mdw213.
[17] Lu U. Biologics Price Competition and Innovation Act: Striking a Delicate Balance Between Innovation and Accessibility. Minn J Law Sci Technol 2014;15:613. https://doi.org/10.24926/15529541.3433.
[18] Fda, Cder. Considerations in Demonstrating Interchangeability With a Reference Product: Update Guidance for Industry DRAFT GUIDANCE. n.d.
[19] Fda, Cder. Promotional Labeling and Advertising Considerations for Prescription Biological Reference Products, Biosimilar Products, and Interchangeable Biosimilar Products Questions and Answers Guidance for Industry. 2025.
[20] Bas TG, Duarte V. Biosimilars in the Era of Artificial Intelligence—International Regulations and the Use in Oncological Treatments. Pharmaceuticals 2024;17:925. https://doi.org/10.3390/ph17070925.
[21] Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU. n.d.
[22] FDA approves first interchangeable biosimilar to Perjeta to treat certain types of breast cancer Action. n.d.

[23] U.S. FDA grants interchangeability designation to Celltrion's denosumab biosimilars, STOBOCLO® (denosumab-bmwo) and OSENVELT® (denosumab-bmwo) _ Press Release _ CelltrionUSA n.d.
[24] FDA Moves to Accelerate Biosimilar Development and Lower Drug Costs. 2025.
[25] ANVISA approves biosimilars for denosumab, trastuzumab, and aflibercept n.d.
[26] Kwon Y, Sarpatwari A, Dusetzina SB. State Substitution Laws and Uptake of an Interchangeable Insulin Biosimilar. JAMA Health Forum 2025;6:e250406. https://doi.org/10.1001/jamahealthforum.2025.0406.